**Citation:**

Ray JG, Kearon C, Yi Q, Sheridan P, Lonn E; Heart Outcomes Prevention Evaluation 2 (HOPE-2) Investigators. Homocysteine-lowering therapy and risk for venous thromboembolism: A randomized trial. *Ann Intern Med.* 2007; 146 (11): 761-767.

**PubMed ID:** 17470822

**Study Design:**

Secondary analysis of data from a randomized trial

**Class:**

A - Click here for explanation of classification scheme.

**Research Design and Implementation Rating:**

POSITIVE: See Research Design and Implementation Criteria Checklist below.

**Research Purpose:**

To determine whether decreasing homocysteine levels altered the risk for symptomatic venous thromboembolism.

**Inclusion Criteria:**

- A history of coronary, cerebrovascular or peripheral vascular diseases
- Diabetes mellitus
- At least one additional risk factor for cardiovascular disease regardless of baseline homocysteine level
- History of venous thromboembolism or the presence or absence of risk factors for venous thromboembolism did not affect eligibility.

**Exclusion Criteria:**

Persons taking daily vitamin supplementation with more than 0.2mg of folic acid.

**Description of Study Protocol:**

**Recruitment**

- The study included 5,522 participants 55 years of age or older
- Subjects from 145 centers in 13 countries were enrolled:
  - Canada (N=3,568)
  - US (N=414)
  - Brazil (N=265)
  - Western European countries (N=426)
  - Slovakia (N=849).

**Design**

A randomized placebo-controlled clinical trial.

**Dietary Intake/Dietary Assessment Methodology**

Not specified, but the paper mentioned that the results of any measurement on changes in blood levels of folate, vitamins $B_6$ and $B_{12}$ and homocysteine were kept confidential.

**Blinding Used**

Information about block size and whether it was random or fixed was kept confidential for all study investigators. The randomization sequence was concealed. All study personnel and study participants were masked to treatment allocation.

**Intervention**

A once-daily supplement containing 2.5mg of folic acid, 50mg of vitamin $B_6$ and 1.0mg of vitamin $B_{12}$.

**Statistical Analysis**

- Intention-to-treat analysis was used to compare the effect of homocysteine-lowering therapy with that of placebo on the subsequent development of venous thromboembolism
- Time-to-event analysis was conducted using a Cox proportional hazards regression model and expressed unadjusted risk as hazard ratios and 95% CI
- Survival curve was estimated using the Kaplan-Meier procedure and treatment groups were compared by a log-rank test
- At each interval clinic visit, follow-up was greater than 99%.

**Data Collection Summary:**

**Timing of Measurements**

- Baseline demographic data; medical history and medication use, including current anticoagulant therapy, were recorded for all participants at study entry
- Baseline homocysteine levels were obtained in 3,306 randomly selected participants (60% of total) who had fasted overnight
- The first evaluation for venous thromboembolism occurred 18 months after randomization. After that, venous thromboembolism was assessed routinely every six months to an average follow-up of five years.

**Dependent Variables**

The primary outcome was symptomatic venous thromboembolism:

- Included deep venous thrombosis or pulmonary embolism (or both)
- Diagnosis of deep venous thrombosis: Required confirmation with duplex leg ultrasonography or venography
- Diagnosis of pulmonary embolism: Required confirmation with ventilation-perfusion lung scanning, computed tomographic pulmonary angiography or conventional pulmonary angiography
- Diagnostic testing had indeterminate results or was not done: Required oral anticoagulant therapy to be initiated at the same time that new-onset venous thromboembolism was recorded on the case report form.

**Independent Variables**

Adherence to treatment: assessed by interview and pill count.

**Description of Actual Data Sample:**

- *Initial N:* 5,522 participants
- *Attrition:* Data on all persons (N=5,522) who were enrolled in the Heart Outcomes Prevention Evaluation 2 (HOPE-2) were included in the current report
- *Age:* 55 years of age or older
- *Ethnicity:* Approximately 3.8% to 3.9% of the sample was of non-white ethnicity
- *Other relevant demographics:* A total of 3,982 participants (72%) were from Canada and the US, where universal food fortification with folic acid was in place before the start of the trial
- *Location:* Subjects were from 145 centers in 13 countries were enrolled, including:
  - Canada (N=3,568)
  - US (N=414)
  - Brazil (N=265)
  - Western European countries (N=426)
  - Slovakia (N=849).

**Summary of Results:**

**Table 1. Baseline Characteristics***

| Characteristic | Homocysteine-Lowering Therapy Group (N=2,758) | Placebo Group (N=2,764) |
|---|---|---|
| **Mean age (SD), y** | 68.8 (7.1) | 68.9 (6.8) |
| **Median follow-up (IQR), person-years** | 5.0 (4.8–5.0) | 5.0 (4.8–5.0) |
| **Women** | 796 (28.9) | 763 (27.6) |
| **Non-white ethnicity** | 106 (3.8) | 109 (3.9) |
| **Living in Canada or the United States** | 1,988 (72.1) | 1,994 (72.1) |

| | | |
|---|---|---|
| **Coronary artery disease** | 2,285 (82.8) | 2,315 (83.8) |
| **Cerebrovascular disease** | 372 (13.5) | 371 (13.4) |
| **Peripheral artery disease** | 216 (7.8) | 169 (6.1) |
| **Current smoking** | 306 (11.1) | 327 (11.8) |
| **Cancer†** | 121 (4.4) | 117 (4.2) |
| **Hypertension** | 1,542 (55.9) | 1,497 (54.2) |
| **Dyslipidemia** | 1,524 (55.3) | 1,526 (55.2) |
| **Diabetes mellitus** | 1,122 (40.7) | 1,087 (39.3) |
| **Aspirin or other antiplatelet therapy** | 2,148 (77.9) | 2,224 (80.5) |
| **Oral anticoagulant therapy** | 227 (8.2) | 193 (7.0) |
| **Lipid-lowering medication** | 1,627 (59.0) | 1,690 (61.1) |
| **Estrogen replacement therapy among women** | 137 (17.2) | 130 (17.0) |
| **Multivitamin use** | 331 (12.0) | 307 (11.1) |
| **Mean geometric plasma homocysteine level (SD), umol per L‡** | 11.5 (1.4) | 11.5 (1.4) |

* Values are expressed as N (%), unless indicated otherwise. IQR = interquartile range.
† All types of cancer, except for non-melanoma skin cancer.
‡ Among the 3,306 participants who had plasma homocysteine measured at baseline.

**Table 2. Rate of Venous Thromboembolism**

| Variable | Incidence of Venous Thromboembolism per 100 Person-Years | | Hazard Ratio (95% CI) | Absolute Risk Difference (95% CI) |
|---|---|---|---|---|
| | Homocysteine-Lowering Therapy Group (N=2,758) | Placebo Group (N=2,764) | | |
| All venous thromboembolism events (N=88)* | 0.35 | 0.35 | 1.01 (0.66 to 1.53) | 0.0025 (-0.1434 to 0.1483) |
| **Location of venous thromboembolism** | | | | |
| Deep venous thrombosis (N=61) | 0.25 | 0.24 | 1.04 (0.63 to 1.72) | 0.0095 (-0.1117 to 0.1307) |
| Pulmonary embolism (N=33)† | 0.13 | 0.13 | 1.14 (0.57 to 2.28) | 0.0088 (-0.0801 to 0.0977) |
| **Type of venous thromboembolism event** | | | | |
| Unprovoked (N=42) | 0.19 | 0.16 | 1.21 (0.66 to 2.23) | 0.0340 (-0.0717 to 0.1397) |

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| Provoked (N=46) | 0.17 | 0.20 | 0.85 (0.47 to 1.51) | -0.0306 (-0.1365 to 0.0753) |

* There were 44 individual cases of venous thromboembolism in each group.
† Six individuals with pulmonary embolism also had deep venous thrombosis.

**Other Findings**

- *Figure 1:* Among the 821 participants whose baseline homocysteine level was in the highest quartile (more than 13.8umol per L), vitamin therapy did not reduce the risk for venous thromboembolism [hazard ratio, 1.71 (95% CI, 0.48 to 6.06)]. For the 2,216 individuals who did not undergo homocysteine sampling at baseline, the hazard ratio was 1.49 (95% CI, 0.79 to 2.80).
- *Figure 2:* Forty-four episodes of venous thromboembolism occurred in each group, corresponding to an incidence rate of 0.35 per 100 person-years in each group [hazard ratio, 1.01 (CI, 0.66 to 1.53); P=0.97]
- *Appendix Table:* The characteristics of participants who were randomly selected to have plasma homocysteine levels assessed at baseline were fairly similar to those of participants who did not have levels assessed, with some notable exceptions. Specifically, fewer participants who underwent homocysteine sampling at baseline were women (25% vs. 33%), and more were from North America (82% vs. 57%) and were taking a lipid-lowering drug (67% vs. 50%).

**Author Conclusion:**

Decreasing homocysteine levels with folic acid and vitamins $B_6$ and $B_{12}$ did not reduce the risk for symptomatic venous thromboembolism.

***Reviewer Comments:***

***Limitations***

- *Venous thromboembolism outcomes were not centrally adjudicated*
- *The first recording of venous thromboembolic events occurred 18 months after study enrollment; nonetheless, nearly 20% of all events occurred during this period*
- *The proportion of participants with a previous episode of venous thromboembolism was not known*
- *The criteria that we used to define venous thromboembolism were more sensitive and specific than those used in the original HOPE-2, resulting in about 0.1% higher incidence in the study*
- *The wide CI of 0.66 to 1.53 for the hazard ratio of deep venous thrombosis may reflect some uncertainty about whether homocysteine treatment was helpful or harmful.*

***Strengths***

- *The HOPE-2 was the largest randomized clinical trial to evaluate the effect of homocysteine-lowering therapy on venous thromboembolism and fewer than 1% of participants were lost to follow-up*
- *The study had a placebo-controlled design and a prospective assessment of venous*

*thromboembolism that included objective confirmation*

- *The analysis focused on the anatomical location of venous thromboembolism (deep venous thrombosis and pulmonary embolism) and whether it was provoked, according to important risk factors, such as age and sex, baseline homocysteine level and the presence of folic acid food fortification.*

*Additionally, the study was a secondary analysis of the HOPE-2 trial, which included older adults at high risk for atherosclerosis, but not those specifically at high risk for venous thromboembolism.*

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***Research Design and Implementation Criteria Checklist: Primary Research***

| **Relevance Questions** | | |
|---|---|---|
| 1. | Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies) | Yes |
| 2. | Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about? | Yes |
| 3. | Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice? | Yes |
| 4. | Is the intervention or procedure feasible? (NA for some epidemiological studies) | Yes |

| **Validity Questions** | | |
|---|---|---|
| **1.** | **Was the research question clearly stated?** | Yes |
| 1.1. | Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified? | Yes |
| 1.2. | Was (were) the outcome(s) [dependent variable(s)] clearly indicated? | Yes |
| 1.3. | Were the target population and setting specified? | Yes |
| **2.** | **Was the selection of study subjects/patients free from bias?** | Yes |
| 2.1. | Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study? | Yes |
| 2.2. | Were criteria applied equally to all study groups? | Yes |
| 2.3. | Were health, demographics, and other characteristics of subjects described? | Yes |
| 2.4. | Were the subjects/patients a representative sample of the relevant population? | Yes |
| **3.** | **Were study groups comparable?** | Yes |
| 3.1. | Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT) | Yes |

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| 3.2. | Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline? | Yes |
| 3.3. | Were concurrent controls used? (Concurrent preferred over historical controls.) | Yes |
| 3.4. | If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis? | N/A |
| 3.5. | If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.) | N/A |
| 3.6. | If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")? | N/A |
| **4.** | **Was method of handling withdrawals described?** | Yes |
| 4.1. | Were follow-up methods described and the same for all groups? | Yes |
| 4.2. | Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.) | Yes |
| 4.3. | Were all enrolled subjects/patients (in the original sample) accounted for? | Yes |
| 4.4. | Were reasons for withdrawals similar across groups? | Yes |
| 4.5. | If diagnostic test, was decision to perform reference test not dependent on results of test under study? | N/A |
| **5.** | **Was blinding used to prevent introduction of bias?** | Yes |
| 5.1. | In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate? | Yes |
| 5.2. | Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.) | Yes |
| 5.3. | In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded? | N/A |
| 5.4. | In case control study, was case definition explicit and case ascertainment not influenced by exposure status? | N/A |
| 5.5. | In diagnostic study, were test results blinded to patient history and other test results? | N/A |
| **6.** | **Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?** | Yes |
| 6.1. | In RCT or other intervention trial, were protocols described for all regimens studied? | Yes |
| 6.2. | In observational study, were interventions, study settings, and clinicians/provider described? | N/A |

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| 6.3. | Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect? | ??? |
| 6.4. | Was the amount of exposure and, if relevant, subject/patient compliance measured? | Yes |
| 6.5. | Were co-interventions (e.g., ancillary treatments, other therapies) described? | No |
| 6.6. | Were extra or unplanned treatments described? | Yes |
| 6.7. | Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups? | Yes |
| 6.8. | In diagnostic study, were details of test administration and replication sufficient? | N/A |
| **7.** | **Were outcomes clearly defined and the measurements valid and reliable?** | Yes |
| 7.1. | Were primary and secondary endpoints described and relevant to the question? | Yes |
| 7.2. | Were nutrition measures appropriate to question and outcomes of concern? | N/A |
| 7.3. | Was the period of follow-up long enough for important outcome(s) to occur? | ??? |
| 7.4. | Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures? | Yes |
| 7.5. | Was the measurement of effect at an appropriate level of precision? | Yes |
| 7.6. | Were other factors accounted for (measured) that could affect outcomes? | Yes |
| 7.7. | Were the measurements conducted consistently across groups? | Yes |
| **8.** | **Was the statistical analysis appropriate for the study design and type of outcome indicators?** | Yes |
| 8.1. | Were statistical analyses adequately described and the results reported appropriately? | Yes |
| 8.2. | Were correct statistical tests used and assumptions of test not violated? | Yes |
| 8.3. | Were statistics reported with levels of significance and/or confidence intervals? | Yes |
| 8.4. | Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? | Yes |
| 8.5. | Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? | Yes |
| 8.6. | Was clinical significance as well as statistical significance reported? | Yes |
| 8.7. | If negative findings, was a power calculation reported to address type 2 error? | No |
| **9.** | **Are conclusions supported by results with biases and limitations taken into consideration?** | Yes |

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| 9.1. | Is there a discussion of findings? | Yes |
| 9.2. | Are biases and study limitations identified and discussed? | Yes |
| **10.** | **Is bias due to study's funding or sponsorship unlikely?** | Yes |
| 10.1. | Were sources of funding and investigators' affiliations described? | Yes |
| 10.2. | Was the study free from apparent conflict of interest? | Yes |